REMARKS

Applicants respectfully request reconsideration of the present application in view of the foregoing amendments and in view of the reasons that follow.

I. Status of the Claims

With this submission, claims 1, 17, and 18 are amended and claim 19 is newly added. Support for these amendments can be found throughout the specification, and specifically on page 20 lines 20-24. No claims are canceled. Hence, upon entry of this paper, claims 1-4 and 6-19 will remain pending with claims 1, 2, 6-9, 13 and 17-19 under active consideration.

This amendment adds, changes and/or deletes claims in this application. A detailed listing of all claims that are, or were, in the application, irrespective of whether the claim(s) remain under examination in the application, is presented, with an appropriate defined status identifier.

II. Claim Objections

The Office objects to claim 18 because it lacks proper subject-verb agreement. Applicants have amended claim 18 to correct this error. Accordingly, Applicants believe the objection is rendered moot.

III. Claim Rejection - 35 U.S.C. §103(a)

Claims 1-2, 6-7, 13 and 17 are rejected as allegedly obvious over Harlow & Lane ("Harlow") in view of Ishikawa et al. (Genomics 26(3):527-34)("Ishikawa"), U.S. 5,623,053 ("Gastinel"), U.S. 5,639,597 ("Lauffer"), U.S. 5,866,693 ("Laping"), U.S. 5,541,087 ("Lo"), US 5,374,533 ("Matsuzawa") and WO 96/22788 ("Browning"). Additionally, claims 8-9 are rejected as obvious over the previously cited references in view of U.S. 5,646,115 ("Frank"). Applicants respectfully traverse the rejection.

A. The Cited References Alone or in Combination Do Not Teach the Invention

None of the cited references, alone or in combination disclose the claimed invention. Specifically, Applicants describe the deficiencies of the cited references in the analysis below.

Ishikawa discloses that HM1.24 is a transmembrane protein. Ishikawa uses a secretory fusion protein of the truncated HM1.24 and the Fc portion of an IgG1. As already mentioned in the reply dated August 13, 2010, the Fc moiety was provided by Dr. Seed and is described in Zettlmeissl et al. (DNA Cell Biol. (1990)9(5): 347-353, "Seed" reference). The Seed reference discloses that a fusion protein with the constant region prolongs the plasma half life. It appears that Ishikawa et al used the fusion protein because of its advantageous properties concerning half-life. Ishikawa et al does not disclose or suggest anything which would motivate a skilled person in the art to remove the Fc portion from the fusion protein.

Gastinel discloses a soluble Fc receptor which was created by removing a transmembrane domain. This truncated Fc receptor was produced by introducing the modified cDNA in selected cells which then secreted the Fc receptor into the medium. The secreted Fc receptor was purified by using an affinity column comprising an antibody to which the receptor can bind. In other words: specific antibodies were selected which had the ability to bind the truncated protein.

Applicants note that the current claims are not directed to an immunoassay for detecting a protein, but for detecting an antibody. Therefore, an antigen protein has to be chosen, which can bind the antibody. None of the cited documents show that the truncated form of HM1.24 has the correct conformation and can still be recognized by the HM1.24 antibody. To the contrary, the prior art (e.g. Ishikawa et al.) discloses only HM1.24 fusion proteins of the soluble protein with an Fc portion.

Matsuzawa discloses an improved immunoassay for determining chondrocalcin, a soluble protein, in body fluids by using an enzyme-labeled mammalian chondrocalcin or anti-chondrocalin antibody. Matsuzawa further mentions that sometimes, if a **known amount of an antigen** to be measured is added to a specimen, the sensitivity necessary **for measuring the antigen** cannot be obtained, or, the exact amount sometimes cannot be determined. Furthermore, "the causes of reactions other than the specific one are not always elucidated thoroughly, but it is understood that these reactions occur ...in case of the presence of

substances such as rheumatoid factor reacting with the Fc moiety of IgG, known as non-specific antibody" (col. 2, line 15-25). Matsuzawa further states:

> In some cases, Fab', F(ab)', or Facb fragments are preferred as the labeled antibody. In other words, first, there exists components bonding to the Fc moiety of the antibody such as the rheumatoid factor and such components cause reactions with nonspecific antibodies other than the target antigen-antibody reaction. Consequently, exact determination of chondrocalcin in body fluid becomes difficult. When the fragment is used as the labeled antibody, however, these reactions do not occur and exact values are given"

Col. 4, lines 41-50.

Although the currently pending claims are drawn to an immunoassay based on antigen-antibody binding, these claims are, as the Office stated, directed to the **detection of an antibody and not an antigen protein**. Matsuzawa teaches avoiding any Fc portion in an immunoassay for the detection of a soluble protein and uses also antibody fragments without the Fc portion. However, the anti-HM1.24 antibody comprises an Fc portion. Consequently, applying Matsuzawa to an immunoassay for detecting an antibody, would leave a skilled artisan to either remove the Fc portion from both the antibody and the antigen, or from neither of them.

Laping discloses that an Fc fusion protein can useful in therapy and diagnosis. However, it might be desirable to remove the Fc portion "when the Fc portion proves to be hindrance to use in therapy and diagnosis, for example, when the fusion protein is to be used as an **antigen for immunizations**" (col. 9, line 55 until col. 10 line 12, emphasis added). Lapling does not disclose or suggest removal of the Fc portion for an immunoassay. In addition, the authors specifically point out that the Fc portion has its advantages and should therefore only be removed when the Fc portion proves a **hindrance.** (See Lapling, col. 10 lines 4-6) Such a hindrance, however, was not known for the HM1.24 protein.

B. Stability is Also Important for *In Vitro* Experiments

The Office stated that serum stability is only of interest in *in vivo* experiments. Applicants respectfully disagree.

It is very well known that body fluids, e.g. blood and serum, contain various enzymes including proteases. The serum stability is of more importance for *in vivo* experiments than for *in vitro* experiments as the duration of drugs in the body is relevant for their efficacy. However, Figure 4 of the "Seed"-Reference shows that even within 1 hour the serum concentration of the Fc fusion protein decreased. On page 350 of the "Seed"-Reference, right column, last paragraph and page 351, left column, first paragraph, it is mentioned that the stability of the fusion proteins is 50 times higher than the one of the soluble protein (without Fc portion). Therefore, the hydrolysis of the soluble protein in serum must be considerable, and even if the protease activity might be smaller under *in vitro* conditions, a skilled person in the art would nonetheless consider it.

Furthermore, the Office stated that Applicants did not provide any evidence to establish that proteolysis occurring in an ELISA assay was a significant or documented problem in the art, for which no remedy or solution was known. However, as Applicants have pointed out, there was a solution for this problem: to use Fc fusion proteins.

In addition, the claims are directed to a detection method of the anti-HM1.24 antibody. The prior art at the time of priority describes the detection of such antibodies in an cell-based ELISA (see e.g. Goto et al, (1994) Blood, 84:1922-30, enclosed) or an ELISA using monoclonal antibodies recognizing specific CL or VL subgroups of the target antibody (see e.g. Ozaki et al, (1997) Blood, 90:3179-86, with reference to Ozaki et al, (1994) Clin Immunol and Immunopath, 71(2): 183-9, enclosed). Although it was known that the HM1.24 is a transmembrane protein, the claimed method was not used. This is a clear indication that it was not obvious to the skilled person to use the soluble part of HM1.24 for detecting the antibody in body fluids with an ELISA assay.

In view of the uncertainties involved with a soluble HM1.24 and the clear advantages of the Fc fusion protein, the skilled person in the art would have chosen either an antibody as

disclosed in Ozaki et al, or an Fc fusion protein for an immunoassay. Matsuzawa would not have motivated a skilled person to remove the transmembrane domain without fusing the soluble protein to an Fc portion. Fc moieties could not be avoided in the assay as the antibody which shall be detected already comprises such a portion.

Finally, Applicants note that Harlow, Lauffer, Browning and/or Frank cannot remedy the deficiencies of Ishikawa, Gastinel, Lapin and/or Matsuzawa. Accordingly, the claims cannot be rendered obvious by any of the cited references alone or in combination.

The inventors show for the first time, that soluble HM1.24 has the ability to form a dimer, and that it is still recognized by the anti HM1.24 antibody. It would not have been obvious to a skilled artisan to use a soluble HM1.24 protein for the detection of the anti-HM1.24 antibody and to increase the sensitivity of the assay and detect the antibody at low concentrations.

Therefore, for at least these reasons, Applicants believe the current claims are not obvious. Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejection.

CONCLUSION

Applicants believe that the present application is now in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested.

The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by a check being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even entirely missing or a credit card payment form being unsigned, providing incorrect information resulting in a rejected credit card transaction, or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicants hereby petition for such extension under 37 C.F.R. §1.136 and authorizes payment of any such extensions fees to Deposit Account No. 19-0741.

Respectfully submitted,

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for

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